Kawasaki disease

Kawasaki disease, also known as **Kawasaki syndrome**, **lymph node syndrome**, and **mucocutaneous lymph node syndrome**,[1] is an autoimmune disease[2] in which the medium-sized blood vessels throughout the body become inflamed. It is largely seen in children under five years of age. It affects many organ systems, mainly those including the blood vessels, skin, mucous membranes, and lymph nodes. Its rarest but most serious effect is on the heart, where it can cause fatal coronary artery aneurysms in untreated children. Without treatment, mortality may approach 1%, usually within six weeks of onset. With treatment, the mortality rate is 0.17% in the U.S.[3]

Often, a pre-existing viral infection may play a role in its pathogenesis.[4] The skin, the conjunctivae of the eyes, and the mucous membranes of the mouth become red and inflamed. Swelling of the hands and feet is often seen and lymph nodes in the neck are often enlarged. A recurrent fever, often 37.8 °C (100.0 °F) or higher, is characteristic of the acute phase of the disease.[5] In untreated children, the fever lasts about 10 days, but may range from five to 25 days.[5] The disorder was first described in 1967 by Tomisaku Kawasaki in Japan.[6]

1 Classification

Systemic vasculitis is an inflammatory condition affecting arteries and veins throughout the body, and is usually caused by a proliferation of cells associated with an immune response to a pathogen, or autoimmunity.[7] Systemic vasculitides may be classified according to the type of cells involved in the proliferation, as well as the specific type of tissue damage occurring within the vein or arterial walls.[7] Under this classification scheme for systemic vasculitis, Kawasaki disease is considered to be a necrotizing vasculitis (also called necrotizing angeititis), which may be identified histologically by the occurrence of necrosis (tissue death), fibrosis, and proliferation of cells associated with inflammation in the inner layer of the vascular wall.[7][8] (Other diseases featuring necrotizing vasculitis include polyarteritis nodosa, granulomatosis with polyangiitis, Henoch-Schönlein purpura, and Churg-Strauss syndrome.[7])

Kawasaki disease may be further classified as a medium-sized-vessel vasculitis, affecting medium- and small-sized blood vessels,[9][10][11] such as the smaller cutaneous vasculature (veins and arteries in the skin) that range from 50 to 100 μm in diameter.[12][13] Kawasaki disease is also considered to be a primary childhood vasculitis, a disorder associated with vasculitis that mainly affects children under the age of 18.[14][15] A recent, consensus-based evaluation of vasculitides occurring primarily in children resulted in a classification scheme for these disorders, to distinguish them and suggest a more concrete set of diagnostic criteria for each.[15] Within this classification of childhood vasculitides, Kawasaki disease is, again, a predominantly medium-sized vessel vasculitis.[15]

It is also an autoimmune form of vasculitis,[5] and is not associated with ANCA antibodies, unlike other vasculitic disorders associated with them (such as granulomatosis with polyangiitis, microscopic polyangiitis, and Churg-Strauss syndrome).[7][16] This categorization is considered essential for appropriate treatment.[17]

2 Signs and symptoms

Kawasaki disease often begins with a high and persistent fever that is not very responsive to normal treatment with paracetamol (acetaminophen) or ibuprofen.[18][19] It is the most prominent symptom in Kawasaki disease, is a characteristic sign of the acute phase of the disease, is normally high (above 39-40 °C), remittent, and is followed by extreme irritability.[19][20] Recently, it is reported to be present in patients with atypical or incomplete Kawasaki disease;[21][22] nevertheless, it is not present in 100% of cases.[23] The first day of fever is considered the first day of illness,[18] and the duration of fever is on average one to two weeks; in the absence of treatment, it may extend for three to four weeks.[5] Prolonged fever is associated with higher incidence of cardiac involvement.[24] It responds partially to antipyretic drugs and does not cease with the introduction of antibiotics.[5] However, when appropriate therapy is started – intravenous immunoglobulin and aspirin – the fever is gone after two days.[25]

Bilateral conjunctival inflammation was reported to be the most common symptom after fever.[26][27] It typically involves the bulbar conjunctivae, is not accompanied by suppuration, and is not painful.[28] It usually begins shortly after the onset of fever during the acute stage of the disease.[18] Anterior uveitis may be present on slit-lamp examination.[29][30] Iritis can occur, too.[31] Keratic precipitates are another eye manifestation (detectable by a slit lamp but are usually too small to be seen by the unaided eye).[18][32]

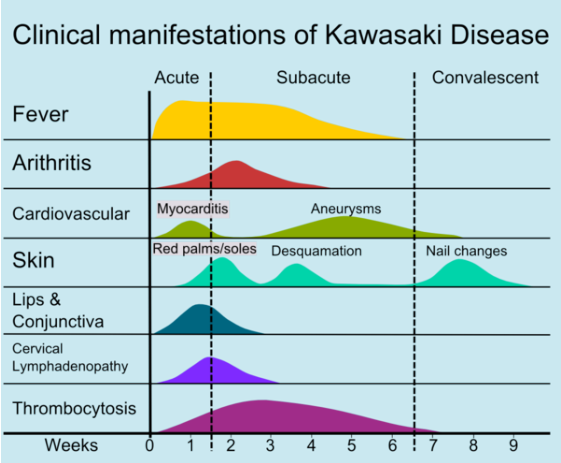
Kawasaki disease presents with set of oral manifestations, the most characteristic changes are the bright red (erythema), swollen lips (edema) with vertical cracking (fissures) and bleeding.[33] The mucosa of the oropharynx may be bright red, and the tongue may have a typical "strawberry tongue" appearance (marked erythema with prominent gustative papillae).[5][13] These oral manifestations are caused by the typical necrotizing microvasculitis with fibrinoid necrosis.[33]

Cervical lymphadenopathy is seen in 50% to 75% of patients, whereas the other features are estimated to occur in 90% of patients,[18][26] but sometimes it can be the dominant presenting symptom.[32][34] According to the definition of the diagnostic criteria, at least one impaired lymph node ≥ 1.5 cm in diameter should be involved.[13] Affected lymph nodes are painless or minimally painful, nonfluctuant, and nonsuppurative; erythema of the neighboring skin may occur.[18] Children with fever and neck adenitis who do not respond to antibiotics should have Kawasaki disease considered as part of the differential diagnoses.[18]

In the acute phase of the disease, changes in the peripheral extremities can include erythema of the palms and soles, which is often striking with sharp demarcation[18] and often accompanied by painful, brawny edema of the dorsa of the hands or feet. This is why affected children frequently refuse to hold objects in their hands or to bear weight on their feet.[5][18] Later, during the convalescent or the subacute phase, desquamation of the fingers and toes usually begins in the periungual region within two to three weeks after the onset of fever and may extend to include the palms and soles.[38] Around 11% of children affected by the disease may continue skin-peeling for many years.[39] One to two months after the onset of fever, deep transverse grooves across the nails may develop (Beau's lines),[40] and occasionally nails are shed.[40]

The most common cutaneous manifestation is a diffuse macular-papular erythematous rash, which is quite nonspecific.[41] The rash varies over time and is characteristically located on the trunk; it may further spread to involve the face, extremities, and perineum.[5] Many other forms of cutaneous lesions have been reported; they may include scarlatiniform, papular, urticariform, multiform-like erythema, and purpuric lesions; even micropustules were reported.[42][43] It can be polymorphic, not itchy, and normally observed up to the fifth day of fever.[44] However, it is never bullous or vesicular.[5]

In the acute stage of Kawasaki disease, systemic inflammatory changes are evident in many organs.[10] Joint pain (arthralgia) and swelling, frequently symmetrical, and arthritis can also occur.[26] Myocarditis,[45] diarrhea,[13] pericarditis, valvulitis, aseptic meningitis, pneumonitis, lymphadenitis, and hepatitis may be present and are manifested by the presence of inflammatory cells in the affected tissues.[10] If left untreated, some symptoms will eventually relent, but coronary artery aneurysms will not improve, resulting in a significant risk of death or disability due to myocardial infarction.[13] If treated quickly, this risk can be mostly avoided and the course of illness cut short.[46]



Clinical manifestations and time course of Kawasaki disease[18][47]

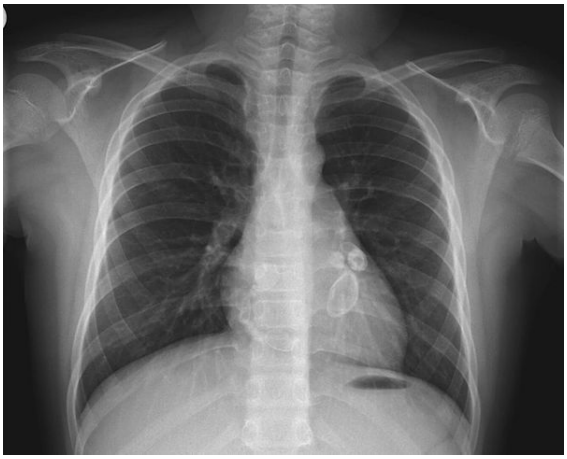
Other reported nonspecific symptoms include cough, rhinorrhea, sputum, vomiting, headache, and seizure.[26]

The course of the disease can be divided into three clinical phases.[13]

- The acute febrile phase, which usually lasts for one to two weeks, is characterized by fever, conjunctival injection, erythema of the oral mucosa, erythema and swelling of the hands and feet, rash, cervical adenopathy, aseptic meningitis, diarrhea, and hepatic dysfunction.[13] Myocarditis is common during this time, and a pericardial effusion may be present.[18] Coronary arteritis may be present, but aneurysms are generally not yet visible by echocardiography.
- The subacute phase begins when fever, rash, and lymphadenopathy resolve at about one to two weeks after the onset of fever, but irritability, anorexia, and conjunctival injection persist. Desquamation of the fingers and toes and thrombocytosis are seen during this stage, which generally lasts until about four weeks after the onset of fever. Coronary artery aneurysms usually develop during this time, and the risk for sudden death is highest.[18][48]
- The convalescent stage begins when all clinical signs of illness have disappeared, and continues until the sedimentation rate returns to normal, usually at six to eight weeks after the onset of illness.[13]

The clinical presentation between adults and children differs, as adults' neck lymph nodes are more affected (93% of adults versus 15% of children), hepatitis (65% versus

10%), and arthralgia (61% versus 24-38%).[13][49] Some patients have atypical presentations and may not have the classical symptoms. This occurs in particular in young infants;[50] those patients are especially at higher risk for cardiac artery aneurysms.[18][51]



X-ray showing aneurysmal enlargement of the coronary arteries, which is a complication in a Kawasaki syndrome

2.1 Cardiac

The cardiac complications are the most important aspect of Kawasaki disease. It is the main cause of heart disease acquired in childhood in the United States and Japan.[13] In developed nations, it appears to have replaced acute rheumatic fever as the most common cause of acquired heart disease in children.[18] Coronary artery aneurysms occur as a sequela of the vasculitis in 20-25% of untreated children.[52] It is first detected at a mean of 10 days of illness and the peak frequency of coronary artery dilation or aneurysms occurs within four weeks of onset.[48] Aneurysms are classified into small (internal diameter of vessel wall <5 mm), medium (diameter ranging from 5–8 mm), and giant (diameter > 8 mm).[13] Saccular and fusiform aneurysms usually develop between 18 and 25 days after the onset of illness.[18] Even when treated with high-dose IVIG regimens within the first 10 days of illness, 5% of children with Kawasaki disease develop at the least transient coronary artery dilation and 1% develop giant aneurysms.[53][54][55] Death can occur due either to myocardial infarction secondary to blood clot formation in a coronary artery aneurysm or to rupture of a large coronary artery aneurysm. Death is most common two to 12 weeks after the onset of illness.[18]

Many risk factors predicting coronary artery aneurysms have been identified,[24] including persistent fever after IVIG therapy,[56][57] low hemoglobin concentrations, low albumin concentrations, high white-blood-cell count, high band count, high CRP concentrations, male sex, and age less than one year.[58] Coronary artery lesions resulting from Kawasaki disease change dynamically with time.[5] Resolution one to two years after the onset of the disease has been observed in half of vessels with coronary aneurysms.[59][60] Narrowing of the coronary artery, which occurs as a result of the healing process of the vessel wall, often leads to significant obstruction of the blood vessel and lead to the heart not receiving enough blood and oxygen.[59] This can eventually lead to heart muscle tissue death (myocardial infarction).[59]

MI caused by thrombotic occlusion in an aneurysmal, stenotic, or both aneurysmal and stenotic coronary artery is the main cause of death from Kawasaki disease.[61] The highest risk of MI occurs in the first year after the onset of the disease.[61] MI in children presents with different symptoms from those in adults. The main symptoms were shock, unrest, vomiting, and abdominal pain; chest pain was most common in older children.[61] Most of these children had the attack occurring during sleep or at rest, and around one-third of attacks were asymptomatic.[18]

Valvular insufficiencies, particularly of mitral or tricuspid valves, are often observed in the acute phase of Kawasaki disease due to inflammation of the heart valve or inflammation of the heart muscle-induced myocardial dysfunction, regardless of coronary involvement.[59] These lesions mostly disappear with the resolution of acute illness,[62] but a very small group of the lesions persist and progress.[63] There is also late-onset aortic or mitral insufficiency caused by thickening or deformation of fibrosed valves, with the timing ranging from several months to years after the onset of Kawasaki disease.[64] Some of these lesions require valve replacement.[65]

2.2 Other

Other Kawasaki disease complications have been described, such as aneurysm of other arteries: aortic aneurysm,[66] with a higher number of reported cases involving the abdominal aorta,[67][68] axillary artery aneurysm,[69] brachiocephalic artery aneurysm,[70] aneurysm of iliac and femoral arteries, and renal artery aneurysm.[5][71] Other vascular complications can occur such as increased wall thickness and decreased distensibility of carotid arteries,[72] aorta,[73] and brachioradial artery.[74] This change in the vascular tone secondary to endothelial dysfunction.[71] In addition, children with Kawasaki disease, with or without coronary artery complications, may have a more adverse cardiovascular risk profile,[74] such as high blood pressure, obesity, and abnormal serum lipid profile.[75]

Gastrointestinal complications in Kawasaki disease are similar to those observed in Henoch-Schönlein purpura,[69] such as: intestinal obstruction,[76] colon swelling,[77] intestinal ischemia,[78] intestinal pseudo-obstruction,[79] and acute abdomen.[80]

Eye changes associated with the disease have been described since the 1980s, being found as uveitis, iridocyclitis, conjunctival hemorrhage,[81][82][83] optic neuritis,[69] amaurosis, and ocular artery obstruction.[84]

It can also be found as necrotizing vasculitis, progressing into peripheral gangrene.[85]

The neurological complications per central nervous system lesions are increasingly reported.[86] The neurological complications found are meningoencephalitis,[87] subdural effusion,[88][89] cerebral hypoperfusion,[90] cerebral ischemia and infarct,[91] cerebellar infarction,[92] manifesting with seizures, chorea, hemiplegia, mental confusion, lethargy and coma,[69] or even a cerebral infarction with no neurological manifestations.[91] Other neurological complications from cranial nerve involvement are reported as ataxia,[69] facial palsy,[93] and sensorineural hearing loss.[94][95] Behavioral changes are thought to be caused by localised cerebral hypoperfusion,[90] can include attention deficits, learning deficits, emotional disorders (emotional lability, fear of night, and night terrors), and internalization problems (anxious, depressive or aggressive behavior).[96][97]

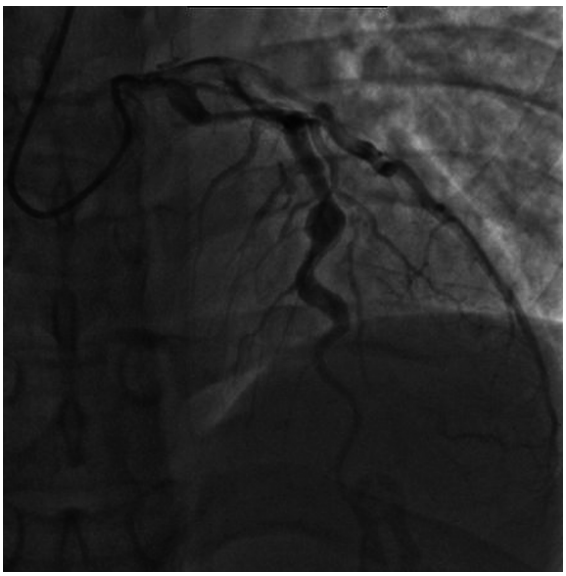
3 Causes

As the cause(s) of Kawasaki disease remain unknown, the illness is more accurately referred to as Kawasaki syndrome. Like all autoimmune diseases, its cause is presumably the interaction of genetic and environmental factors, possibly including an infection. The specific cause is unknown,[98][99][100] but current theories center primarily on immunological causes. Evidence increasingly points to an infectious etiology,[101] but debate continues on whether the cause is a conventional antigenic substance or a superantigen.[102] Researchers at Boston Children's Hospital reported, "some studies have found associations between the occurrence of Kawasaki disease and recent exposure to carpet cleaning or residence near a body of stagnant water; however, cause and effect have not been established."[103]

Other data show a clear correlation between Kawasaki disease and tropospheric wind patterns; winds blowing from central Asia correlate with Kawasaki disease cases in Japan, Hawaii, and San Diego.[104] This association with tropospheric winds has been shown to be modulated at seasonal and interannual timescales by the El Niño–Southern Oscillation phenomenon,[105] further indicating the agent responsible for the disease is a wind-borne pathogen. Efforts are underway to identify the suspected pathogen in air-filters flown at altitude above Japan.[106]

An association has been identified with an SNP in the *ITPKC* gene, which codes an enzyme that negatively regulates T-cell activation.[107] Regardless of where they are living, Japanese children are more likely than other children to manifest the disease, which suggests genetic susceptibility.[103] The HLA-B51 serotype has been found to be associated with endemic instances of the disease.[108]

4 Diagnosis



Angiography showing ectatic LAD, with largest aneurysm = 6.5 mm in diameter

Kawasaki disease can only be diagnosed clinically (i.e., by medical signs and symptoms). No specific laboratory test exists for this condition. It is difficult to establish the diagnosis, especially early in the course of the illness, and frequently children are not diagnosed until they have seen several health-care providers. Many other serious illnesses can cause similar symptoms, and must be considered in the differential diagnosis, including scarlet fever, toxic shock syndrome, juvenile idiopathic arthritis, and childhood mercury poisoning (infantile acrodynia).

Classically, five days of fever[110] plus four of five diagnostic criteria must be met to establish the diagnosis. The criteria are:

1. erythema of the lips or oral cavity or cracking of the lips
2. rash on the trunk
3. swelling or erythema of the hands or feet
4. red eyes (conjunctival injection)
5. swollen lymph node in the neck of at least 15 mm

Many children, especially infants, eventually diagnosed with Kawasaki disease, do not exhibit all of the above criteria. In fact, many experts now recommend treating for Kawasaki disease even if only three days of fever have passed and at least three diagnostic criteria are present, especially if other tests reveal abnormalities consistent with Kawasaki disease. In addition, the diagnosis can be made purely by the detection of coronary artery aneurysms in the proper clinical setting.

4.1 Investigations

A physical examination will demonstrate many of the features listed above.

Blood tests

- Complete blood count may reveal normocytic anemia and eventually thrombocytosis.
- Erythrocyte sedimentation rate will be elevated.
- C-reactive protein will be elevated.
- Liver function tests may show evidence of hepatic inflammation and low serum albumin.

Other optional tests include:

- Electrocardiogram may show evidence of ventricular dysfunction or, occasionally, arrhythmia due to myocarditis.
- Echocardiogram may show subtle coronary artery changes or, later, true aneurysms.
- Ultrasound or computerized tomography may show hydrops (enlargement) of the gallbladder.
- Urinalysis may show white blood cells and protein in the urine (pyuria and proteinuria) without evidence of bacterial growth.
- Lumbar puncture may show evidence of aseptic meningitis.
- Angiography was historically used to detect coronary artery aneurysms, and remains the gold standard for their detection, but is rarely used today unless coronary artery aneurysms have already been detected by echocardiography.
- Temporal artery biopsy

5 Treatment

Children with Kawasaki disease should be hospitalized and cared for by a physician who has experience with this disease. When in an academic medical center, care is often shared between pediatric cardiology, pediatric rheumatology, and pediatric infectious disease specialists (although no specific infectious agent has been identified as yet).[103] Treatment should be started as soon as the diagnosis is made to prevent damage to the coronary arteries.

Intravenous immunoglobulin (IVIG) is the standard treatment for Kawasaki disease[111] and is administered in high doses with marked improvement usually noted within 24 hours. If the fever does not respond, an additional dose may have to be considered. In rare cases, a third dose may be given to the child. IVIG by itself is most useful within the first seven days of onset of fever, in terms of preventing coronary artery aneurysm.

Salicylate therapy, particularly aspirin, remains an important part of the treatment (though questioned by some)[112] but salicylates alone are not as effective as IVIG. Aspirin therapy is started at high doses until the fever subsides, and then is continued at a low dose when the patient returns home, usually for two months to prevent blood clots from forming. Except for Kawasaki disease and a few other indications, aspirin is otherwise normally not recommended for children due to its association with Reye's syndrome. Because children with Kawasaki disease will be taking aspirin for up to several months, vaccination against varicella and influenza is required, as these infections are most likely to cause Reye's syndrome.[113]

Corticosteroids have also been used,[114] especially when other treatments fail or symptoms recur, but in a randomized controlled trial, the addition of corticosteroid to immune globulin and aspirin did not improve outcome.[115] Additionally, corticosteroid use in the setting of Kawasaki disease is associated with increased risk of coronary artery aneurysm, so its use is generally contraindicated in this setting. In cases of Kawasaki disease refractory to IVIG, cyclophosphamide and plasma exchange have been investigated as possible treatments, with variable outcomes.

IL-1 Receptor antagonist (anakinra) can prevent coronary lesion in the mouse KD model. This prevention shows even with three-days-delay in treatment in mice.[116]

Treatments exist for iritis and other eye symptoms. Another treatment may include the use of infliximab. Infliximab works by binding tumour necrosis factor alpha.[117]

6 Prognosis

With early treatment, rapid recovery from the acute symptoms can be expected, and the risk of coronary artery aneurysms is greatly reduced. Untreated, the acute symptoms of Kawasaki disease are self-limited (*i.e.* the patient will recover eventually), but the risk of coronary artery involvement is much greater. Overall, about 2% of patients die from complications of coronary vasculitis. Patients who have had Kawasaki disease should have an echocardiogram initially every few weeks, and then every one or two years to screen for progression of cardiac involvement.

Laboratory evidence of increased inflammation combined with demographic features (male sex, age less than six months or greater than eight years) and incomplete response to IVIG therapy create a profile of a high-risk patient with Kawasaki disease.[58][118] The likelihood that an aneurysm will resolve appears to be determined in large measure by its initial size, in

which the smaller aneurysms have a greater likelihood of regression.[119][120] Other factors are positively associated with the regression of aneurysms, including being younger than a year old at the onset of Kawasaki disease, fusiform rather than saccular aneurysm morphology, and an aneurysm location in a distal coronary segment.[60] The highest rate of progression to stenosis occurs among those who develop large aneurysms.[5] The worst prognosis occurs in children with giant aneurysms.[121] This severe outcome may require further treatment such as percutaneous transluminal angioplasty,[122] coronary artery stenting,[123] bypass grafting,[124] and even cardiac transplantation.[125]

A relapse of symptoms may occur soon after initial treatment with IVIG. This usually requires rehospitalization and retreatment. Treatment with IVIG can cause allergic and nonallergic acute reactions, aseptic meningitis, fluid overload and, rarely, other serious reactions. Overall, life-threatening complications resulting from therapy for Kawasaki disease are exceedingly rare, especially compared with the risk of nontreatment. Also, evidence indicates Kawasaki disease produces altered lipid metabolism that persists beyond clinical resolution of the disease.

7 Epidemiology

Kawasaki disease affects boys more than girls, with people of Asian ethnicity, particularly Japanese and Korean people, most susceptible, as well as people of Afro-Caribbean ethnicity. The disease was rare in Caucasians until the last few decades, and incidence rate fluctuates from country to country.

Currently, Kawasaki disease is the most commonly diagnosed pediatric vasculitis in the world. By far, the highest incidence of Kawasaki disease occurs in Japan, with the most recent study placing the attack rate at 218.6 per 100,000 children <5 years of age (about one in 450 children). At this present attack rate, more than one in 150 children in Japan will develop Kawasaki disease during their lifetimes.

However, its incidence in the United States is increasing. Kawasaki disease is predominantly a disease of young children, with 80% of patients younger than five years of age. About 2,000-4,000 cases are identified in the U.S. each year (9 to 19 per 100,000 children younger than 5 years of age).[103][126][127]

In the United Kingdom, estimates of incidence rate vary because of the rarity of Kawasaki disease. However, it is believed to affect fewer than one in every 25,000 people.[128] Incidence of the disease doubled from 1991 to 2000, however, with four cases per 100,000 children in 1991 compared with a rise of eight cases per 100,000 in 2000.[129]

8 History

The disease was first reported by Tomisaku Kawasaki in a four-year-old child with a rash and fever at the Red Cross Hospital in Tokyo in January 1961, and he later published a report on 50 similar cases.[130] Later, Kawasaki and colleagues were persuaded of definite cardiac involvement when they studied and reported 23 cases, of which 11 (48%) patients had abnormalities detected by an electrocardiogram.[131] In 1974, the first description of this disorder was published in the English-language literature.[132] In 1976, Melish et al. described the same illness in 16 children in Hawaii.[133] Melish and Kawasaki had independently developed the same diagnostic criteria for the disorder, which are still used today to make the diagnosis of classic Kawasaki disease.

A question was raised whether the disease only started during the period between 1960 and 1970, but later a preserved heart of a seven-year-old boy who died in 1870 was examined and showed three aneurysms of the coronary arteries with clots, as well as pathologic changes consistent with Kawasaki disease.[134] Kawasaki disease is now recognized worldwide. In the United States and other developed nations, it appears to have replaced acute rheumatic fever as the most common cause of acquired heart disease in children.[135]

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10 External links

- Kawasaki disease - Stanford Children's Health
- Kawasaki disease research program
- Kawasaki disease foundation
- Kawasaki disease information from Seattle Children's Hospital Heart Center

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11.1 Text

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